

corresponding portion is no more than 15% larger or smaller than SEQ ID No.

35.

156. (new) An isolated nucleic acid that has at least 60% sequence identity to a corresponding portion of the isolated nucleic acid of Claim 9, where the corresponding portion is no more than 15% larger or smaller than SEQ ID No.

35.--

B17  
cancel

#### REMARKS

Prior to this Amendment, claims 1-9, 57, 58, 88-101, 142-146, 148, and 149 were pending. By this Amendment, claims 1-8, 57, 58, 97, 100, 101, 142-144, 146, 148, and 149 have been canceled. New claims 150-156 have been added. Therefore, claims 9, 88-96, 98, 99, 145, and 150-156 are now pending.

Claims 9, 88, 89, 91, 95, 96, 98, 99, and 145 have been amended to more particularly point out and distinctly claim the invention.

Claim 9 has been placed in independent form and has been amended in accord with the Restriction Requirement to delete mention of non-elected inventions.

Claim 88 has been amended to change its dependency from canceled claim 1 to claim 9.

Claim 89 has been amended to recite "nucleic acid molecule" rather than "protein or polypeptide" in accordance with the change in dependency of claim 88, from which claim 89 depends.

Claim 91 has been amended to change its dependency from canceled claim 1 to claim 9.

Claim 95 has been amended to more accurately reflect its antecedent basis.

Claim 96 has been amended to recite “SEQ ID No. 35” in accord with the Restriction Requirement.

Claim 98 has been amended to recite “SEQ ID No. 36” in accord with the Restriction Requirement.

Claim 99 has been amended to change its dependency from canceled claim 97 to claim 98.

Claim 145 has been placed in independent form and has been amended to recite “SEQ ID No. 36” in accord with the Restriction Requirement.

New claims 150 and 151 recite “the entire calicheamicin gene cluster.” Support for this limitation is found in the specification at page 7, lines 1-2.

New claim 152 recites “a corresponding portion,” “high stringency conditions,” and “no more than 15% larger or smaller than SEQ ID No. 35.” Support for these limitations is found in the specification at page 39, lines 15-23 (a corresponding portion), page 38, lines 13-17 (high stringency conditions), page 39, line 23 (no more than 15% larger or smaller than SEQ ID No. 35).

New claims 153-156 recite the above limitations of new claim 152 as well as limitations with respect to percentage sequence identity. Support for these limitations is found in the specification at page 9, lines 16-20 (90% sequence identity, new claim 153), page 9, line 20 to page 10, line 1 (80% sequence identity, new claim 154), page 10, lines 1-4 (70% sequence identity, new claim 155), and page 10, lines 4-8 (60% sequence identity, new claim 156).

No new matter has been added to the amendments to the claims or by the new claims.

Enclosed herewith is a set of corrected Drawings.

The Examiner required that the specification be amended to substitute the phrases “encoding” or “coding for” for the phrase “encoding for.” The specification has been so amended.

#### The rejection under 35 U.S.C. §101

Claims 1-9, 57, 58, 88-99, 145, 146, and 148 were rejected because the specification allegedly “fails to disclose a substantial utility for the CalS gene product” since “the utility of the CalS gene product is not clear other than the CalS gene being implicated in the calicheamicin pathway based on its sequence homology to P450-oxidases.” (Office Action, page 4)

The Applicants disagree with this rejection and ask that it be withdrawn for the reasons that follow. The Applicants submit that these reasons are applicable to the claims as presently pending as well as to the claims pending when this rejection was issued.

#### The legal test for utility

The Utility Examination Guidelines (1242 O.G. 162-168; January 30, 2001) state that the test for whether a claimed invention has patentable utility turns on whether the applicant’s assertion of utility for the claimed invention is specific, substantial, and credible. The present claims pass this test.

#### Specific utility

There are numerous specific assertions of utility for the CalS gene in the present application. Page 36, lines 6-8, teaches that CalS is a P450-oxidase. Figures 5 and 10 show that oxidases such as CalS perform an important step in the

biosynthesis of nucleotide sugars. Figure 11 shows how CalS co-operates with other members of the calicheamicin gene cluster in a biosynthetic pathway.

The paragraph bridging pages 14 and 15 teaches that the CalS gene, since it encodes a P-450 oxidase, may be used in methods of producing calicheamicin analogs. Page 16, lines 3-6 teaches that the CalS gene may be cloned into bacterial strains that make compounds related to calicheamicin, in order to make related compounds. Page 16, line 6 to page 17, line 8, teaches that the CalS gene may be used in methods of combinatorial biosynthesis, in order to generate new drug leads.

Since all of these assertions of utility for CalS pertain to particular functions and particular uses, they are specific assertions of utility.

#### Substantial utility

The specific assertions of utility referred to above are substantial. P-450 oxidases such as CalS have patentable, and therefore substantial, utility. See, e.g., U.S. Patents Nos. 6,133,417; 6,130,077; and 5,801,024 (Exhibits A, B, and C, respectively), which claim P-450 oxidases or genes encoding them.

As discussed above, the present specification teaches that the CalS gene can be used to make calicheamicin related compounds. It is well settled that calicheamicin related compounds have substantial, real-world utility. In fact, one such compound, MyloTarg®, has been approved by the FDA to treat acute myelogenous leukemia (see the specification, at page 3, lines 20-22). Since the CalS gene can be used to make compounds that have substantial utility, the CalS gene itself has substantial utility.

#### Credible utility

The assertion that CalS is a P-450 oxidase is credible. The Applicants wish to point out that this assignment of function is based on more than just an isolated

comparison of CalS and known P450-oxidases. The Applicant has discovered that the CalS gene is part of a large cluster of related metabolic genes linked together in the *Micromonospora echinospora* genome that are involved in the synthesis of calicheamicin. The specification (page 24, last sentence to page 25, first sentence) teaches that it is known in the art that similar clusters of metabolic genes are known in other organisms. Such knowledge would lead one skilled in the art to be confident of sequence homology-derived function assignments for genes in such clusters. When a single gene of unknown function is compared to a single gene of known function, the result is perhaps subject to doubt. However, when a large number of genes of unknown function, linked together in a genome in a way that virtually guarantees they are part of a certain metabolic pathway, are compared to a large number of genes of known function from similar pathways in other organisms, the results of the individual comparisons reinforce each other, making the individual results highly probable.

The present application reports the results of comparisons of multiple genes in the disclosed calicheamicin pathway with multiple genes from other, known, similar pathways. This reinforces the conclusions derived from the individual sequence comparisons of the calicheammicin pathway genes to the point where such conclusions are clearly credible.

This is especially so since, in the case of certain of the linked *M. echinospora* calicheamicin pathway genes, the Applicants have provided experimental data that confirms the assignment of function derived from sequence comparisons. For example, the assignment of function to CalH was confirmed experimentally. Page 31, line 14 to page 32, line 17; Example 5, page 46 to page 47; and Figure 7 show that heterologous expression of CalH in *S. venezuela* demonstrated that CalH was able to

rescue a 4-dehydratase mutant strain, enabling the mutant strain to produce new antibiotics. This work provides indisputable support for the CalH gene assignment. The assignment of function for CalC was also confirmed experimentally. Example 4, page 45 to page 46, provides data that demonstrate that the assignment of function to CalC is correct.

This success in assigning the functions of CalH and CalC would lead one skilled in the art to believe that the functions assigned to the other genes of the calicheamicin pathway are also correct. This reinforces the conclusion that the assignment of function to CalS is credible.

The Applicants submit that the above discussion shows that the present specification discloses that the CalS gene has patentable utility. Therefore, it is respectfully requested that this rejection be withdrawn.

#### The rejections under 35 U.S.C. §112

##### Enablement

Claims 1-9, 57, 58, 88-99, 145, 146, and 148 were rejected for alleged lack of enablement. To the extent this rejection might be applied to the present claims, the Applicants traverse for the following reasons.

The Examiner argued that the prior art teaches that assignments of function based on sequence similarity alone are uncertain, and, since the only teaching with respect to CalS in the application is allegedly the sequence of CalS, “it would be unpredictable to extrapolate the function of [the] CalS gene from its structure alone and would require undue experimentation on the part of a skilled artisan to use the invention.” (Office Action, page 8, lines 4-6)

The basis for this rejection appears to be the belief that the specification inadequately teaches a function for the CalS gene product. The flaw in this analysis is that it views the CalS gene in isolation. It assumes that the only evidence for CalS gene function comes from a comparison of the CalS gene with known P-450 oxidases. This overlooks the fact that the CalS gene is part of a large cluster of metabolic genes linked together in the *M. echinospora* genome. As explained above, this makes the assignment of function for each member of the linked genes of the cluster far more certain than such assignments would be if the genes of the cluster were not so linked.

In view of this, undue experimentation would not be necessary to determine the function of the CalS gene or to use the CalS gene. Therefore, it is respectfully requested that this rejection be withdrawn.

#### Written description

Claim 6 was rejected for alleged lack of written description.

The basis for this rejection is that “the claim encompasses all sequences that hybridize with a DNA comprising the sequence set forth in SEQ ID NO:35 and these sequences have not been described in sufficient detail in the specification to satisfy the written description requirement.” (Office Action, page 10, last line to page 11, line 3)

Claim 6 has been canceled. New claim 152 is directed to nucleic acids that hybridize under conditions of high stringency with the isolated nucleic acid of claim 9. Therefore, the Applicants submit that this rejection does not apply to new claim 152 since the nucleic acids claimed in new claim 152 do not encompass all sequences that hybridize to the nucleic acid of claim 9 since, by virtue of the limitation with respect to high stringency, nucleic acid sequences encompassed by new claim 152

must necessarily be highly similar in structure to the nucleic acid of claim 9. High stringency conditions are defined in the specification at page 38, lines 13-17.

In view of the above, it is respectfully requested that this rejection be withdrawn.

#### Indefiniteness

Claims 1-9, 57, 58, 88-99, 145, 146, and 148 were rejected for indefiniteness because they are directed to unelected inventions.

All of the present claims are drawn to the CalS gene, the elected invention, and do not recite any other sequences from the calicheamicin gene cluster. Therefore, it is respectfully requested that this rejection be withdrawn.

#### The rejections under 35 U.S.C. §102

Claim 6 was subject to the following anticipation rejections:

Claim 6 was rejected under 35 U.S.C. §102(a) as being anticipated by International Patent Publication WO 97/08323.

The basis for this rejection is that WO 97/08323 discloses a sequence having a 17 nucleotide homology with SEQ D NO:35 that is therefore capable of hybridizing to SEQ D NO:35.

Claim 6 was rejected under 35 U.S.C. §102(a) as being anticipated by U.S. Patent No. 5,763,165.



The basis for this rejection is that U.S. Patent No. 5,763,165 discloses an oligonucleotide having a 15 nucleotide homology to SEQ D NO:35 that is therefore capable of hybridizing to SEQ D NO:35.

Claim 6 was rejected under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 5,512,444.

The basis for this rejection is that U.S. Patent No. 5,512,444 discloses an oligonucleotide having a 15 nucleotide homology to SEQ D NO:35 that is therefore capable of hybridizing to SEQ D NO:35.

Claim 6 was rejected under 35 U.S.C. §102(ab) as being anticipated by International Patent Publication WO 95/23874.

The basis for this rejection is that WO 95/23874 discloses a sequence having a 15 nucleotide homology with SEQ D NO:35 that is therefore capable of hybridizing to SEQ D NO:35.

Claim 6 was rejected under 35 U.S.C. §102(b) as being anticipated by International Patent Publication WO 91/16334.

The basis for this rejection is that WO 971/16334 disclose a sequence having a 16 nucleotide homology with SEQ D NO:35 that is therefore capable of hybridizing to SEQ D NO:35.

Claim 6 was rejected under 35 U.S.C. §102(b) as being anticipated by Kunst et al., 1997, Nature 390:249-256.

The basis for this rejection is that Kunst et al. discloses a sequence having a 24 nucleotide homology to SEQ D NO:35 that is therefore capable of hybridizing to SEQ D NO:35.

Claim 6 was rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 5,985,571.

The basis for this rejection is that U.S. Patent No. 5,985,571 discloses an oligonucleotide having a 15 nucleotide homology to SEQ D NO:35 that is therefore capable of hybridizing to SEQ D NO:35.

Claim 6 has been canceled. Thus, it is respectfully requested that this rejection be withdrawn.

The Applicant submits that these anticipation rejections do not apply to new claims 152-156. All of the above anticipation rejections rely on the disclosure in the cited references of nucleotide sequences that might be expected to hybridize to CalS (though not necessarily under high stringency conditions) and that are between 15 and 24 nucleotides long. Given that new claims 152-156 are directed to nucleic acids that hybridize under stringent conditions to SEQ ID No. 35 (new claim 152) or that are 90%, 80%, 70%, or 60% identical in sequence to SEQ ID No. 35 (new claims 153-156) and that also are “no more than 15% larger or smaller than SEQ ID No. 35,” (new claims 152-156) the sequences in the cited references fall outside the scope of new claims 152-156 since they are too short to satisfy the latter limitation. SEQ ID No. 35 is 1,209 nucleotides long. Since 15% of 1,209 equals 181,<sup>1</sup> only nucleic acids which have a sequence of nucleotides that is between 1,028 and 1,390 nucleotides

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<sup>1</sup> Rounded off to the nearest whole nucleotide.

long (1,209 ± 181) and that either hybridizes to SEQ ID No. 35 under stringent conditions or is 90%, 80%, 70%, or 60% identical to SEQ ID No. 35 satisfy the limitations of the new claims.

The time for responding to the Office Action was set for October 30, 2002. Enclosed is a Petition for the Extension of Time under 37 C.F.R. § 1.136(a) for a period sufficient to permit the filing of this response.

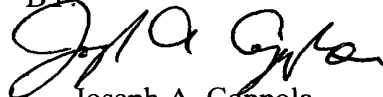
The Applicants hereby also make a Conditional Petition for any relief available to correct any defect seen in connection with this filing, or any defect seen to be remaining in this application after this filing. The Commissioner is authorized to charge Kenyon & Kenyon's Deposit Account No. 11-0600 for any fees associated with such Conditional Petition.

### **CONCLUSION**

In view of the foregoing amendments and remarks, Applicant respectfully submits that all of the pending claims of the subject application are in condition for allowance. Prompt reconsideration and allowance of the present application is therefore earnestly solicited.

Respectfully submitted,

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IN THE SPECIFICATION:

Paragraph beginning at page 1, line 1

*Micromonospora echinospora* genes [encoding] coding for biosynthesis of calicheamicin and self-resistance thereto

Paragraph beginning at page 1, line 9

The present invention relates to a biosynthetic gene cluster of *Micromonospora echinospora* spp. *calichensis*. In particular, the calicheamicin biosynthetic gene cluster contains genes [encoding] coding for proteins and enzymes used in the biosynthetic pathway and construction of calicheamicin's aryltetrasaccharide and aglycone, and the gene conferring calicheamicin resistance. The present invention also relates to isolated genes of the biosynthetic cluster and their corresponding proteins. In addition, the invention relates to DNA hybridizing with the calicheamicin gene cluster and the isolated genes of that cluster. The invention also relates to expression vectors containing the biosynthetic gene cluster, the individual genes, or functional variants thereof.

Paragraph beginning at page 6, line 3

Calicheamicin's molecular architecture in conjunction with its useful biological activity and potential therapeutic value brand calicheamicin [an] a target for the study of natural product biosynthesis. While the radical-based mechanism of oxidative DNA cleavage by calicheamicin (i.e. aromatization of the bicyclo[7.3.1]tridecadiynene core structure, via a 1,4-dehydrobenzene-diradical,

resulting in the site specific oxidative double strand DNA cleavage) is well understood, it was unknown, prior to this invention, how *Micromonospora* constructs calicheamicin. As a result, before the present invention, there was a need to discover and understand calicheamicin biosynthesis. Prior to this discovery of the present inventors, knowledge of genes [encoding] coding for nonchromoprotein enediyne biosynthesis was completely lacking.

Paragraph beginning at page 6, line 13

The toxicity of the enediyne compounds, including calicheamicin, centers on the problem of directing the compound to [the] cleave only the DNA of interest, such as tumor cell DNA, and not the DNA of the host. Due to calicheamicin's powerful ability to cleave DNA, scientists have investigated the mechanism by which calicheamicin-producing organism protects itself against the DNA-cleaving activity of the molecule[.] (Rothstein, D. M., *Enediyne Antibiotics as Antitumor Agents*, p. 77 (1995)). Prior to this invention, knowledge of genes [encoding] coding for non-chromoprotein enediyne self resistance was completely lacking.

Paragraph beginning at page 25, line 15

The second screening was based on the assumption that calicheamicin's biosynthetic cluster would also contain genes [encoding] coding for deoxysugar ligand synthesis. Further, it was postulated that all hexopyranosyl ligands of calicheamicin diverged from the common intermediate 4-keto-6-deoxy TDP-D-glucose (30), Figure 5, as macromolecule-sugar synthesis in many organisms began with a similar common intermediate. Thus, it was believed that the cluster [encoding] coding for calicheamicin biosynthesis, in addition to carrying a PKS-encoding region,

would carry both a common glucose-1-phosphate nucleotidyltransferase and a NDP- $\alpha$ -D-glucose 4,6-dehydratase gene, encoding the putative enzymes E<sub>p1</sub>, and E<sub>od</sub>, respectively. See figure 5. These enzymes are necessary to convert a sugar (12)(figure 5) to the hypothesized common intermediate, 4-keto-6-deoxy TDP-D-glucose (30). Analogs to 4,6-dehydratases have been previously characterized from *E. coli*, *Salmonella*, and *Streptomyces*. Additionally, a nucleotide transferase from *Salmonella* has been characterized as an [alpha]  $\alpha$ -D-glucose-1-phosphate thymidyltransferase. The secondary screen was performed using a probe based upon the postulation that the *M. echinospora*'s calicheamicin synthesis would begin from a similar precursor found in *E. coli*, *Streptomyces* and *Salmonella*, and that this precursor required a dehydratase to convert it into the common intermediate, 4-keto-6-deoxy TDP-D-glucose (30). In particular, a DNA probe (designated E<sub>od</sub><sup>I</sup>) was designed from the conserved NAD<sup>+</sup>-binding site of bacterial NDP- $\alpha$ -D-glucose 4,6-dehydratases. He, X., et al., *Biochem.*, 35, 4721-4731 (1996). Southern hybridization of the genomic *M. echinospora* cosmid library with the E<sub>od</sub><sup>I</sup> probe revealed cross-hybridization with clones 4b, 10a, 13a, 56, and 60. Two additional clones, designated 58 and 66, were also identified in this screen. See Figure 1. This secondary hybridization indicated the clustering of genes encoding both polyketide and deoxysugar biosynthesis.

Paragraph beginning at page 27, line 5

The clones positive for PKS I and II and deoxy sugar biosynthesis homology and calicheamicin resistance were used to map the biosynthetic cluster. Southern hybridization established similarity between clones 3a, 4a, 4b, 10a, 13a, 16a and 56. In addition, nucleotide sequence overlaps were found between clones 4b, 13a, and 56.

See Figure 1. Restriction mapping and Southern hybridization of these clones indicated that the positive cosmid clones corresponded to a continuous region of the *M. echinospora* chromosome spanning > 100 kb. The present invention thus provides for cosmids having a nucleic acid molecule from *Micromonospora echinospora* [encoding] coding for a nonchromoprotein enediyne biosynthetic cluster.

Paragraph beginning at page 28, line 20

The *calC* locus was isolated by identifying calicheamicin genomic cosmid clones that were able to grow on [luria bertani] Luria Bertani ("LB") agar plates containing ampicillin and calicheamicin. The DNA of the positive clones (clones that grew on the plates containing calicheamicin) was isolated and subsequent restriction mapping localized the desired phenotype (calicheamicin resistance). The DNA was then sequenced and the open reading frames analyzed to ascertain the [orf] ORF encoding for the desired phenotype. *In vitro* studies were also performed and confirmed the ability of CalC to inhibit DNA cleavage.

Paragraph beginning at page 29, line 4

DNA containing *calC* was cloned into an inducible vector, using known methods, resulting in overexpression of *calC*. The polypeptide product (CalC) was then isolated and purified to homogeneity. Analysis of the purified CalC revealed that it is a non-heme iron metalloprotein that functions via inhibition of calicheamicin-induced DNA cleavage *in vitro*. Another aspect of the invention is an expression vector containing *calC* or a fragment of *calC* encoding for a bioactive molecule. There is also provided a transformed host cell, preferably bacteria, more preferably *E. coli*, containing *calC* or a fragment of *calC* [encoding] coding for a bioactive

molecule. Such transgenic expression of *calC* results in an  $10^5$ -fold increase in calicheamicin resistance in *E.coli*, a 100-fold increase in resistance in *S.lividans*, and a 50-fold increase in resistance in yeast.

Paragraph beginning at page 35, line 5

One aspect of the invention relates to an isolated DNA strand containing the *calG* gene and having the DNA sequence SEQ ID. NO.: 5. Another aspect of the invention is the protein, CalG, having amino acid sequence SEQ ID. No.: 6. According to BLAST analysis, *calG* encodes a 4,6-dehydratase. Dehydratases had been characterized from *E. coli*, *Salmonella* and *Streptomyces*, (Thompson, M. et al., *J. Gen. Microbiol.*, 138, 779-786 (1992); Vara, J.A., et al., *J. Biol. Chem.*, 263, 14992-14995 (1988)), and analogous NDP-D-glucose 4,6-dehydratases had been characterized from a variety of organisms. Liu, H.-w., et al., *Ann. Rev. Microbiol.*, 48, 223-256 (1994); Hallis, T.M., et al., *Acc. Chem. Res.*, in press (1999). Based upon these prior studies, it was known that the overall transformation catalyzed by 4,6-dehydratases is an intramolecular oxidation-reduction where an enzyme-bound  $\text{NAD}^+$  receives the 4-H as a hydride in the oxidative half-reaction and passes the reducing equivalents to C-6 of the dehydration product in the reductive half-reaction. Thus, it appears that Cal G is necessary for the formation of the aryltetrasaccharide 4,6-dideoxy-4-hydroxylamino-D-glucose moiety. CalG appears to be a TDP-D-glucose 4,6-dehydratase which catalyzes the conversion of intermediate 13 into intermediate 30. (See figure 5). Another aspect of the invention is an expression vector containing *calG* or a fragment of *calG* [encoding] coding for a bioactive molecule. There is also provided a transformed host cell, preferably bacteria, more preferably, *E. coli*, containing *calG* or a fragment of *calG* [encoding] coding for a bioactive molecule.



Paragraph beginning at page 36, line 6

There is also disclosed an isolated DNA strand containing the *calS* gene. Based on sequence homology with other P450-oxidases, CalS appears to be a P450-oxidase homolog which performs the oxidation of intermediate 39 to intermediate 42 (figure 5). The oxidation may occur at the nucleotide sugar level or hydroxylamine formation after the sugar has been transferred to the aglycone. There is also provided an expression vector containing the *calS* gene or a fragment of *calS* encoding for a bioactive molecule. There is also provided a transformed host cell, preferably bacteria, more preferably *E. coli*, containing *calG* or a fragment of *calG* [encoding] coding for a bioactive molecule.

Paragraph beginning at page 36, line 22

There is also provided an expression vector containing the *calQ* gene or a fragment of *calQ* encoding for a bioactive molecule. There is also provided a transformed host cell, preferably bacteria, more preferably *E. coli*, containing *calQ* or a fragment of *calQ* [encoding] coding for a bioactive molecule.

**IN THE CLAIMS:**

9. (twice amended) [The] An isolated nucleic acid molecule [of Claim 1], wherein said nucleic acid molecule comprises [at least one of] SEQ ID No.[1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33,] 35[, 37, 39, 41, 43, 45, 47, 49, 51,

53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93 or 94].

88. (amended) An expression vector comprising [a] said nucleic acid molecule [encoding a protein or biologically active fragment of a protein, wherein said nucleic acid molecule is a nucleic acid molecule] of Claim [1] 9.
89. (amended) The expression vector of Claim 88, wherein said nucleic acid molecule is operably linked to regulatory sequences to control expression of said [protein or polypeptide] nucleic acid molecule.
91. (amended) A host cell transformed with the nucleic acid molecule of Claim [1] 9.
95. (amended) The host cell of Claim 91, wherein [the host bacteria] said bacterium is *E. coli* or *Streptomyces*.
96. (amended) A cosmid comprising [an isolated] a nucleic acid molecule from [a nonchromoprotein enediyne] the calicheamicin biosynthetic gene cluster from *Micromonospora echinospora*, wherein said [isolated] nucleic acid molecule comprises [said nucleic acid molecule, a portion or portions of said nucleic acid molecule wherein said portion or portions encode a protein or proteins, a portion or portions of said nucleic acid molecule wherein said portion or portions encode a biologically active fragment of a protein or proteins, a single-stranded nucleic acid molecule derived from said nucleic acid molecule, or a single-stranded

nucleic acid molecule derived from a portion or portions of said nucleic acid molecule] SEQ ID No. 35.

98. (amended) A method of expressing a protein comprising the steps of transfecting a host cell with the expression vector of Claim 88 and incubating said cell for a length of time and under conditions sufficient for expression of [a desired quantity of] said protein [or said biologically active fragment of a protein] wherein said protein comprises SEQ ID No.36.

99. (amended) The method of Claim [97] 98, wherein said host cell is a [bacterium] bacterial, yeast, insect, plant, [fungi] fungus, or mammalian cell.

145. (amended) [The] An isolated nucleic acid molecule [of claim 1, wherein said protein comprises] coding for [at least one of] an amino acid sequence comprising SEQ ID [Nos.:] No. [2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34,] 36[, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, or 95].